

REMARKS

Enclosed is a check for \$510 for the requisite fee for a three-month extension of time. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1, 3-8, 10-12, 14-32, 34, 35 and 37-42 are currently pending in this application. Claims 1 and 37-41 are amended herein and new claim 42 is added.

Claims 1 and 37-41 are amended for clarity to specify that the hydrostatic delivery system includes a homogeneous mixture of the hydrostatic couple and the agent of interest. Support for this amendment is provided throughout the specification (*e.g.*, see page 9, line 20 and page 26, lines 22-26).

Claims 1 and 37-41 also are amended to specify that the agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Support for this amendment is provided throughout the specification (*e.g.*, see page 15, lines 17-20 and page 26, lines 10-13).

Claim 1 further is amended to delete the features relating to the weight ratio of the components of the hydrostatic delivery system. The features deleted from claim 1 have been made the subject of new claim 42.

Claims 37-41 are amended to specify that the one, or more than one hydrodynamic fluid imbibing polymer and the one, or more than one hydrostatic pressure modulating agent are cross-linked. Support for the amendment is provided throughout the specification (*e.g.*, see page 5, lines 11-17; page 15, lines 23-26; and page 19, lines 13-23). Claim 37 also is amended to clarify that the amylose and dextran contain diester or diether crosslinks. Based on page 17, lines 21-24 and page 18, lines 19-24 of the description, it is clear that *each* of the amylose, dextran, pullulan succinates and glutarates contain diester or diether crosslinks.

Claims 38 and 39 are amended to specify that the hydrostatic delivery system is in the form of a solid compact. Support for the amendment is found throughout the specification (*e.g.*, page 23, lines 6-16). Claims 38 and 39 also are amended to state that the agent is released when the system comes into contact with an external fluid. Basis for the amendment is found throughout the specification (*e.g.*, page 23, line 31 through page 26, line 13).

Basis for added claim 42 is found throughout the specification (*e.g.*, see Tables 1-7 on pages 28-34). No new matter is added.

REJECTION OF CLAIM 37 UNDER 35 U.S.C. § 102(b) OVER BAI

Claim 37 is rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,840,329 (Bai). The Examiner alleges that Bai discloses a dosage form that includes dextran and a cross-linked polyvinylpyrrolidone, and thus discloses every element of claim 37. Applicant respectfully traverses the rejection.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir., 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 37 is directed to a hydrostatic delivery system that includes a homogeneous mixture of: a) an agent of interest; and b) a hydrostatic couple, comprising: i) one, or more than one *cross-linked* hydrodynamic fluid-imbibing polymer comprising one, or more than one compound selected from the group consisting of amylose containing diester or diether crosslinks, dextran containing diester or diether crosslinks, pullulan succinate containing diester or diether crosslinks, pullulan glutarates containing diester or diether crosslinks, and a combination thereof; and ii) one, or more than one *cross-linked* hydrostatic pressure modulating agent, wherein the agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics following administration of the delivery system.

DISCLOSURE OF BAI

Bai discloses a pulsatile drug delivery system including three distinct groups of particles, with each group having an inner controlled release core containing diltiazem,

Carbopol 971P and non-crosslinked dextran; a swelling layer that may contain diltiazem, and an external coating layer containing Carbopol 971P (see Example 9). Each group of particles displays a distinct pattern of drug release.

ANALYSIS

The instantly claimed hydrostatic delivery system includes a homogeneous mixture of an agent of interest, one, or more than one cross-linked hydrodynamic fluid-imbibing polymer comprising one, or more than one compound selected from the group consisting of amylose containing diester or diether crosslinks, dextran containing diester or diether crosslinks, pullulan succinate containing diester or diether crosslinks, pullulan glutarates containing diester or diether crosslinks, and a combination thereof; and one, or more than one cross-linked hydrostatic pressure modulating agent.

The dosage form of Bai includes a plurality of particles enclosed in a tablet or capsule, where the particles are divided into several delivery units. Each group of delivery units has its own unique inner structured active core and specific external coating. These particles contain a hydrogel controlled-release matrix layer for delivering controlled prolonged pulsed-doses, and a swelling agent for a rapid release layer for delivering recurring short, pulsed-doses. None of the particles or layers within the particles include amylose containing diester or diether crosslinks, dextran containing diester or diether crosslinks, pullulan succinate containing diester or diether crosslinks, pullulan glutarates containing diester or diether crosslinks, or a combination thereof. Thus, Bai does not disclose every element of the claimed subject matter, and thus does not anticipate claim 37. Reconsideration and withdrawal of the rejection are respectfully requested.

REJECTION OF CLAIMS 38 AND 39 UNDER 35 U.S.C. § 102(b) OVER DRESDNER Jr. *et al.*

Claims 38 and 39 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,357,636 (Dresdner, Jr. *et al.*). The Examiner alleges that Dresdner, Jr. *et al.* discloses an antiseptic composition that includes antiseptic agents such as povidone iodine, sodium hypochlorite, surfactant, antibiotics, bicarbonate or peroxide and viscosity modifying polymers such as cross-linked polyvinylpyrrolidone and Carbopol and thus allegedly discloses every element of claims 38 and 39. Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 38 is directed to a hydrostatic delivery system that includes a homogeneous mixture of an agent of interest; a hydrostatic couple comprising one or more than one cross-linked hydrodynamic fluid-imbibing polymer and one or more than one cross-linked hydrostatic pressure modulating agent; and an expansion source including an oxygen precursor selected from the group consisting of sodium percarbonate, sodium perborate monohydrate, anhydrous sodium perborate, effervescent perborate and sodium dichloroisocyanurate. The hydrostatic delivery system is in the form of a solid compact and the agent of interest is released with a zero-order or near zero-order release kinetics when the hydrostatic delivery system comes into contact with an external fluid.

Claim 39 is directed to a hydrostatic delivery system that includes a homogenous mixture of an agent of interest; a hydrostatic couple, comprising one or more than one cross-linked hydrodynamic fluid-imbibing polymer and one or more than one cross-linked hydrostatic pressure modulating agent; and an expansion source comprising an chlorine dioxide precursor selected from the group consisting of sodium hypochlorite and calcium hypochlorite. The hydrostatic delivery system is in the form of a solid compact and the agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics when the hydrostatic delivery system comes into contact with an external fluid.

DISCLOSURE OF DRESDNER, JR. *et al.*

Dresdner, Jr. *et al.* discloses a glove that contains a non-liquid antiseptic composition including an antiseptic, such as sodium hypochlorite (column 27, line 45), sodium perborate (column 27, line 48), an antiviral agent, a viricidal agent, a bactericidal agent, an antifungal agent, an antiparasitic agent (column 27, lines 28-32), or a mixture thereof; and a viscosity-modifying polymer or agent, such as cross-linked polyvinylpyrrolidone polymers (column 35, line 61) and Carbopol[®] 934 (column 36, line 37), or a mixture thereof. The non-liquid antiseptic composition of Dresdner, Jr. *et al.* is contained in a compartment of a flexible glove, and if the glove is punctured by an object, the antiseptic composition inside the compartment within the glove is transferred onto the hand and into the hand wound caused by the object puncturing the glove wall. Dresdner, Jr. *et al.* discloses that this provides an immediate and automatic antiseptic treatment of the contaminated hand and hand wound (column 1, lines 35-40). Dresdner, Jr. *et al.* discloses that its antiseptic can be in the form of a dry solid, a granular, a crystalline, a powder, a foam, a paste, a gel, an ointments, or a grease that can adhere to some degree to an object puncturing the glove (col. 20, lines 29-52).

ANALYSIS

Dresdner, Jr. *et al.* discloses that its antiseptic is in a non-liquid form, such as a dry solid, a granular, a crystalline or a powder, that can adhere to some degree to an object puncturing the glove. Dresdner, Jr. *et al.* does not disclose a hydrostatic delivery system that includes a homogeneous mixture of an agent of interest and a hydrostatic couple in the form of a solid compact. Dresdner, Jr. *et al.* does not disclose that the agent of interest is released from its antiseptic composition with a zero-order or near zero-order release kinetics when the hydrostatic delivery system comes into contact with an external fluid. Thus, Dresdner, Jr. *et al.* does not disclose every element of the claimed subject matter, and thus does not anticipate claims 38 and 39. Reconsideration and withdrawal of the rejection are respectfully requested.

REJECTION OF CLAIMS 1, 3-8, 10-12, 14-32, 34, 35, 40 and 41 UNDER 35 U.S.C. § 103(a) OVER FRITSCH *et al.* IN VIEW OF THORMAR *et al.* or PATHER *et al.*

Claims 1, 3-8, 10-12, 14-32, 34, 35, 40 and 41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,213,794 (Fritsch *et al.*) in view of U.S. Patent No. 6,596,763 (Thormar *et al.*) or U.S. Patent No. 6,200,604 (Pather *et al.*). The Examiner alleges that Fritsch *et al.* teaches a composition that includes polycarbophil and a cross-linked acrylate polymer that is not cross-linked with allylsucrose or allylpentaerythritol, but alleges that Thormar *et al.* teaches that polycarbophil and Carbopol are gelling agents and that Pather *et al.* teaches that polycarbophil and Carbopol are bioadhesives, and thus one gelling agent or bioadhesive can be substituted for by another. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to prepare the dosage of Fritsch *et al.* using polycarbophil and Carbopol. Applicant respectfully traverses the rejection.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103(a), there must be (1) some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)); and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed

invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). “To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher” *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). MPEP 2143 states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference . . . must teach or suggest all the claim limitations.

In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

THE CLAIMS

Claim 1 is directed to a hydrostatic delivery system that includes a homogeneous mixture of a hydrostatic couple and an agent of interest, where the hydrostatic couple includes one, or more than one hydrodynamic fluid-imbibing polymer comprising one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol, and one, or more than one hydrostatic pressure-modulating agent comprising one, or more than one crosslinked polyvinylpyrrolidone, and where the agent of interest is released with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of

the hydrostatic delivery system. Claims 3-8, 10-12, 14-32, 34 and 35 ultimately depend from claim 1 and are directed to various embodiments thereof.

Claim 40 is directed to a hydrostatic delivery system that includes a homogeneous mixture of an agent of interest and a hydrostatic couple comprising i) one or more than one cross-linked hydrodynamic fluid-imbibing polymer and ii) one or more than one cross-linked hydrostatic pressure modulating agent. The system includes an enteric coating containing one, or more than one pH sensitive barrier polymer. The agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

Claim 41 is directed to a hydrostatic delivery system that includes a homogeneous mixture of an agent of interest and a hydrostatic couple comprising i) one or more than one cross-linked hydrodynamic fluid-imbibing polymer and ii) one or more than one cross-linked hydrostatic pressure modulating agent, where the hydrostatic delivery system is a matrix extrusion spheroid. The agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

TEACHINGS OF THE CITED REFERENCES

FRITSCH *et al.* (US 5,213,794)

Fritsch *et al.* teaches an antacid dosage form having a long gastric residence time, characterized in that the dosage form contains antacid active compounds that are agglomerated with calcium polycarbophil to form granules and the granules are bound together in a tablet using water-soluble anionic polymers (see column 3, lines 55-59). One of the dosage forms taught by Fritsch *et al.* includes granules containing an antacid agglomerated with calcium polycarbophil (a calcium salt of polyacrylic acid crosslinked with divinyl glycol) and the granules are bound together in a tablet using crospovidone (cross-linked polyvinylpyrrolidone) (see Example 1, column 6, lines 19-54). The dosage forms of Fritsch *et al.* are administered as chew tablets (see column 5 line 33), or dissolve rapidly (see column 5 lines 27-34 and column 6 lines 50-54) resulting in the liberation of the granule particles, which adhere to the gastric mucosa (*e.g.* column 5, lines 10-16 and column 6, lines 52-53).

THORMAR *et al.* (US 6,596,763).

Thormar *et al.* teaches a hydrogel formulation for topical application to skin or mucosal membranes that includes at least one microbiocidal lipid, at least one solubilizing

agent which keeps the lipid dissolved in the formulation and a gel-forming agent. Thormar *et al.* teaches a hydrogel formulation for topical application to skin or mucosal membranes. The formulation includes at least one microbiocidal lipid, at least one solubilizing agent which keeps the lipid dissolved in the formulation and a gel-forming agent. The formulations are designed to deliver the microbiocidal lipid to a mucosal membrane, such as vaginal mucosa, for fast and immediate action of the microbiocidal lipid or lipids in prevention of infection in connection with sexual intercourse (col. 5m lines 19-31). Thormar *et al.* teaches that the formulation is applied to the vaginal mucosa at the most 1 hour before sexual intercourse, preferably between 5 and 45 minutes before sexual intercourse (col. 5, lines 32-29). Thormar *et al.* teaches that its formulation releases between 25% to 50% of the drug within one hour (col. 10, lines 34-41). Thormar *et al.* teaches the drug release characteristics of its formulations (see FIGS. 1, 2 and 3). Thormar *et al.* teaches that gelling agents useful in its hydrogel formulation include cellulose such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose and carboxymethylcellulose and salts thereof; acrylic polymers such as polyacrylic acids and polymethacrylates, *e.g.*, Carbopol[®], poly(hydroxyethyl methacrylate), poly(methoxyethyl methacrylate) and poly(methoxyethoxyethyl methacrylate); proteins such as gelatin; polyvinyl alcohols; polyethylene glycols, optionally cross-linked, with an average molecular weight from about 20,000 to about 4,000,000; and polyvinylpyrrolidone with an average molecular weight in the range from 10,000 to 700,000 (column 6, lines 20-35).

PATHER *et al.* (US 6,200,604)

Pather *et al.* teaches a pharmaceutical dosage form adapted to supply a medicament to the oral cavity for buccal, sublingual or gingival absorption of the medicament. The dosage form contains an orally administerable medicament in combination with an effervescent for use in promoting absorption of the medicament in the oral cavity (col. 1, lines 15-20). Pather *et al.* teaches its dosage forms include excipient fillers to assist in the rapid dissolution of the dosage form in the mouth (col. 5, lines 26-29). Pather *et al.* teaches that its dosage form spontaneously begins to disintegrate due to the moisture in the mouth and that the disintegration and the effervescence stimulates additional salivation which further enhances disintegration (col. 5, lines 54-58). Pather *et al.* teaches that Carbopol[®] 934P, sodium carboxymethyl cellulose, methylcellulose, polycarbophil, hydroxypropylmethyl cellulose, sodium alginate and sodium hyaluronate are bioadhesives (column 4, lines 36-38).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

Claim 1

The hydrostatic delivery system of claim 1 includes a homogenous mixture of an active ingredient in combination with one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol (hydrodynamic fluid-imbibing polymer) and one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone (hydrostatic pressure modulating agent), where the hydrostatic delivery system releases the agent of interest with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

a. An acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol

Fritsch *et al.* teaches a dosage form that includes calcium polycarbophil. Calcium polycarbophil is the calcium salt of polyacrylic acid crosslinked with divinyl glycol. Calcium polycarbophil is not an acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol. The Examiner states that the polycarbophil of Fritsch *et al.* differs from the cross-linked acrylate that is cross-linked with allylsucrose or allylpentaerythritol (see Office Action, page 5). Thus, Fritsch *et al.* does not teach or suggest an acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol.

b. Homogeneous mixture

In addition, Applicant respectfully submits that Fritsch *et al.* does not teach or suggest a composition that includes a homogenous mixture of an active ingredient in combination with one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol (hydrodynamic fluid-imbibing polymer) and one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone (hydrostatic pressure modulating agent). Fritsch *et al.* teaches that its antacid preparations are characterized in that they contain antacid active compounds that are agglomerated with calcium polycarbophil to form granules, and that the granules are bound together in compressed tablets, using water-soluble anionic polymers as binders. Thus, the antacid active, calcium polycarbophil and water-soluble anionic polymers (such as crospovidone shown in Example I) of Fritsch *et al.* are not a homogeneous mixture.

c. Zero-order or near zero-order release kinetics

Also, Fritsch *et al.* does not teach or suggest a delivery system that releases the agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a

therapeutically practical time period following administration of the delivery system. The "delivery system" of Fritsch *et al.* is designed to easily disintegrate on contact with an aqueous medium so that the agglomerates containing the antacid or active agent can quickly be dispersed so that they can freely distribute and adhere to the gastric mucosa. Thus, the components used in Fritsch *et al.* do not result in a controlled release of the active agent, but rather results in a rapid disintegration of the tablet (less than two minutes) liberating calcium polycarbophil granules containing the active agent (Column 6, lines 50-54). Thus, Fritsch *et al.* does not teach or suggest a homogeneous mixture that includes an agent of interest, one or more than one hydrodynamic fluid-imbibing polymer comprising acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol, and one or more than one hydrostatic pressure modulating agent comprising a homopolymer of a cross-linked polyvinyl-pyrrolidone, where the hydrostatic delivery system releases the agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Applicant respectfully submits that neither Thormar *et al.* nor Pather *et al.* teaches or suggests the elements missing from the teachings of Fritsch *et al.*

Thormar *et al.*

Thormar *et al.* teaches a hydrogel formulation containing a microbiocidal lipid for topical application to skin or mucosal membranes. Thormar *et al.* teaches that the formulations release between 25% to 50% of the drug within one hour. Thormar *et al.* provides exemplary drug release characteristics of its formulations in FIGS. 1-3. None of the drug release curves taught by Thormar *et al.* demonstrates zero-order or near zero-order release kinetics. Thormar *et al.* does not teach or suggest a formulation that produces a steady-state efflux of an agent of interest over a period of time at a constant rate that is concentration independent. Thus, Thormar *et al.* does not teach or suggest a hydrostatic delivery system that releases the agent of interest with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Further, Thormar *et al.* teaches that Carbopol[®], povidone K29-32, carboxymethylcellulose, hydroxypropylmethylcellulose, and polycarbophil are gelling agents. Thormar *et al.* does not teach that calcium polycarbophil is a gelling agent, nor does the reference teach or suggest replacing calcium polycarbophil in a formulation with Carbopol[®] or provide any motivation for doing so. Therefore, combining the teaching of Fritsch *et al.* with the teachings of Thormar *et al.* does not teach or suggest every element of claim 1. Claims 3-8, 10-12, 14-32, 34 and 35 ultimately depend from claim 1 and

include the limitations thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claims 1, 3-8, 10-12, 14-32, 34, 35.

Pather *et al.*

Pather *et al.* does not teach or suggest the elements missing from the teaching of Fritch *et al.* Pather *et al.* teaches that its dosage forms include effervescent agents to promote absorption of the medicament in the oral cavity and that its dosage forms spontaneously begin to disintegrate due to the moisture in the mouth. The disintegration of the dosage form and the effervescence stimulates additional salivation, which further enhances disintegration. Thus, the dosage form of Pather *et al.* does not provide a controlled release of the active agent, but rather rapidly disintegrates, resulting in the near instantaneous release of all of the active ingredient in the oral cavity. Thus, Pather *et al.* does not teach or suggest a hydrostatic delivery system that releases the agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Further, Pather *et al.* does not teach that calcium polycarbophil is a bioadhesive agent, nor does the reference teach or suggest replacing calcium polycarbophil in a formulation with Carbopol® or provide any motivation for doing so. Therefore, combining the teaching of Fritch *et al.* with the teachings of Pather *et al.* does not result in the hydrostatic delivery system as instantly claimed.

Proposed combination would change the principle of operation

Further, Applicant respectfully submits that modifying the compositions of Fritch *et al.* to do what Applicant has done would change the principle of operation of the Fritch *et al.* composition. The instantly claimed hydrostatic delivery system releases the agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. The composition of Fritch *et al.* rapidly disintegrates, dispersing granules of antacid active compounds agglomerated with calcium polycarbophil from the composition so that the granules can freely distribute and adhere to the gastric mucosa. Reformulating the composition of Fritch *et al.* so that the dosage form provides a controlled release of the active ingredient in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system would eliminate the rapid dispersion of individual granules agglomerated with active ingredients

throughout the gastric mucosa. Thus, the proposed combination of the prior art would change the principle of operation of the prior art invention being modified (Fritsch *et al.*).

Hence, the combination of the teachings of Fritch *et al.* and Thormar *et al.* or the combination of the teachings of Fritch *et al.* and Pather *et al.* does not teach or suggest every element of claim 1. Because claims 3-8, 10-12, 14-32, 34 and 35 ultimately depend from claim 1 and include the limitations thereof, the Examiner has failed to set forth a *prima facie* case of obviousness for claims 1, 3-8, 10-12, 14-32, 34 and 35.

2. Claim 40

Claim 40 is directed to a hydrostatic delivery system that includes a homogeneous mixture of an agent of interest and a hydrostatic couple, comprising: i) one, or more than one cross-linked hydrodynamic fluid-imbibing polymer; and ii) one, or more than one cross-linked hydrostatic pressure modulating agent; and an enteric coating containing one, or more than one pH sensitive barrier polymers, where the agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

As discussed above, none of Fritch *et al.*, Thormar *et al.* or Pather *et al.*, alone or in any combination, teaches or suggests a hydrostatic delivery system that releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. The dosage forms of Fritch *et al.* and Pather *et al.* are to be chewed or are designed to readily disintegrate. The hydrogels of Thormar *et al.* rapidly release the microbiocidal lipid within an hour and do not have zero-order or near zero-order release kinetics.

Further, claim 40 includes as an element that the hydrostatic delivery system includes an enteric coating. Fritch *et al.* teaches dosage forms that are chewable and rapidly disintegrate upon exposure to gastric fluid, releasing the agglomerated antacid/calcium polycarbophil granules, which bioadhere to the gastric mucosa, resulting in a prolonged gastric exposure. Fritch *et al.* does not teach or suggest an enteric coating. Applicant respectfully submits that neither Thormar *et al.* nor Pather *et al.* teaches or suggests an enteric coating, an element missing from the teachings of Fritsch *et al.*

Thormar *et al.*

Thormar *et al.* teaches hydrogels that are to be applied topically to mucosal membranes. There is no teaching or suggestion in Thormar *et al.* to include an enteric coating in its hydrogel formulation. Thus, combining the teaching of Fritch *et al.* with the teachings of

Thormar *et al.* does not result in the hydrostatic delivery system of claim 40. Neither Fritch *et al.* nor Thormar *et al.*, singly or in combination, teaches or suggests a hydrostatic delivery system that includes an enteric coating and releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claim 40.

Pather *et al.*

Pather *et al.* teaches that its dosage form includes effervescent agents to promote absorption of the medicament in the oral cavity and that its dosage forms spontaneously begins to disintegrate due to the moisture in the mouth. There is no teaching or suggestion in Pather *et al.* to include an enteric coating in its dosage forms. Thus, combining the teaching of Fritch *et al.* with the teachings of Pather *et al.* does not result in the hydrostatic delivery system of claim 40. Neither Fritch *et al.* nor Pather *et al.*, singly or in combination, teaches or suggests a hydrostatic delivery system that includes an enteric coating and releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claim 40.

3. Claim 41

Claim 41 is directed to a hydrostatic delivery system that includes a homogeneous mixture of an agent of interest and a hydrostatic couple, comprising one, or more than one cross-linked hydrodynamic fluid-imbibing polymer and one, or more than one cross-linked hydrostatic pressure modulating agent, where the hydrostatic delivery system is a matrix extrusion spheroid, and the agent of interest is released in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

As discussed above, none of Fritch *et al.*, Thormar *et al.* or Pather *et al.*, alone or in any combination, teaches or suggests a hydrostatic delivery system that releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. The dosage forms of Fritch *et al.* and Pather *et al.* are to be chewed or are designed to readily disintegrate. The hydrogels of Thormar *et al.* rapidly release the microbiocidal lipid within an hour and do not have zero-order or near zero-order release kinetics.

Further, claim 41 includes as an element that the hydrostatic delivery system is a matrix extrusion spheroid. Fritch *et al.* teaches dosage forms that are agglomerated antacid/calcium polycarbophil granules. Fritsch *et al.* teaches that the dosage forms are prepared by customary agglomeration techniques. Fritch *et al.* does not teach or suggest a dosage form that is a matrix extrusion spheroid. Applicant respectfully submits that neither Thormar *et al.* nor Pather *et al.* teaches or suggests a dosage form that is a matrix extrusion spheroid, an element missing from the teachings of Fritsch *et al.*

Thormar *et al.*

Thormar *et al.* teaches hydrogels that are to be applied topically to mucosal membranes. There is no teaching or suggestion in Thormar *et al.* of a dosage form that is a matrix extrusion spheroid. Thus, combining the teaching of Fritch *et al.* with the teachings of Thormar *et al.* does not result in the hydrostatic delivery system of claim 41. Neither Fritch *et al.* nor Thormar *et al.*, singly or in combination, teaches or suggests a hydrostatic delivery system that is a matrix extrusion spheroid and releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claim 41.

Pather *et al.*

Pather *et al.* teaches that its buccal tablets are compressed quarter inch diameter biconvex tablets and that its sublingual tablets are compressed three-eighths inch diameter biconvex tablets, and that the dimensions were chosen to give a comfortable fit in the respective part of the oral cavity for which they were designed (column 6, lines 42-46). There is no teaching or suggestion in Pather *et al.* of a dosage form that is a matrix extrusion spheroid. Thus, combining the teaching of Fritch *et al.* with the teachings of Pather *et al.* does not result in the hydrostatic delivery system of claim 41. Neither Fritch *et al.* nor Pather *et al.*, singly or in combination, teaches or suggests a hydrostatic delivery system that is a matrix extrusion spheroid that releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claim 41.

REBUTTAL TO EXAMINER'S ARGUMENTS

1. "One gelling agent or bioadhesive can be substituted for by another"

The Examiner alleges that Thormar *et al.* and Pather *et al.* teach that polycarbophil and Carbopol are gelling agents and are bioadhesives. The Examiner states that "one gelling agent or bioadhesive can be substituted for by another." It is respectfully submitted that no evidence is provided to support the Examiner's position. The Examiner is reminded that MPEP 2144.03 states:

The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970).

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. *In re Malcolm*, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

If this position is maintained, the Examiner must provide a reference supporting this position.

Further, applicant respectfully submits that the Examiner has not properly characterized the teachings of Fritsch *et al.* in the argument for combining the teachings of Fritsch *et al.* with the teachings of Thormar *et al.* or Pather *et al.* The Examiner states that because Thormar *et al.* and Pather *et al.* teach that polycarbophil and Carbopol are gelling agents or bioadhesives, one of ordinary skill in the art would substitute Carbopol for the polycarbophil of Fritsch *et al.* with the expectation of producing a dosage form having the desired gastric retention time. Fritsch *et al.* does not teach or suggest using *polycarbophil* in its formulations. Fritsch *et al.* teaches compositions that include agglomerated *calcium polycarbophil*. Thormar *et al.* and Pather *et al.* relate the properties of *neutral* polycarbophil to Carbopol. Neither Thormar *et al.* nor Pather *et al.* teaches or suggests that *calcium* polycarbophil and Carbopol are equivalent. Thus, the premise upon which the Examiner's combination of the teachings of Fritsch *et al.* with Thormar *et al.* or with Pather *et al.* is incorrect.

REJECTION OF CLAIMS 1, 3-8, 10-12, 14-32, 34, 35, 40 AND 41 UNDER 35 U.S.C. § 103(a) OVER RORK *ET AL.* IN VIEW OF CONTE *ET AL.*

Claims 1, 3-8, 10-12, 14-32, 34, 35, 40 and 41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,582,838 (Rork *et al.*) in view of U.S. Patent No. 5,780,057 (Conte *et al.*). The Examiner alleges that Rork teaches a tablet formulation that

includes active ingredients such as ranitidine, excipients such as polyvinylpyrrolidone, Carbopol and carbonates, but does not teach or suggest cross-linked polyvinylpyrrolidone, but alleges that Conte *et al.* cures this defect because Conte *et al.* teaches a formulation containing ranitidine and cross-linked polyvinylpyrrolidone. The Examiner alleges that it is *prime facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the very same purpose. Applicant respectfully traverses the rejection for the reasons set forth below.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

TEACHINGS OF RORK *ET AL.* (US 5,582,838)

Rork *et al.* teaches a device that includes an inner core of two layers, one containing a beneficial agent and a polymer that forms microscopic beads when hydrated and the other layer including a polymer that forms microscopic beads when hydrated, and these layers are coated with a water insoluble impermeable polymeric coating (col. 3, lines 30-43). Rork *et al.* teaches a composition that includes nifedipine, Carbopol 974P (a carboxypolymethylene of acrylic acid crosslinked with allyl ethers of sucrose or pentaerythritol), and Povidone K-90 (polyvinylpyrrolidone; see Example 2, column 13, lines 18-59), which is used as an excipient. Rork *et al.* teaches that the release rate of the active agent is controlled by the number, size and configuration of the apertures cut in the insoluble coating of the core (col. 11, lines 31-36).

TEACHINGS OF CONTE *ET AL.* (US 5,780,057)

Conte *et al.* teaches a multi-layer pharmaceutical composition that includes (i) a swellable layer that includes Carbopol 934 PH and cross-linked polyvinylpyrrolidone in a 1:1 wt. ratio, (ii) a controlled release layer that includes ranitidine hydrochloride, hydroxypropyl methylcellulose and polyvinylpyrrolidone, and (iii) a fast release layer that includes ranitidine hydrochloride, polyvinylpyrrolidone and cross-linked polyvinylpyrrolidone (see Example 4). Conte *et al.* teaches the rapid and considerable swelling of the swellable layer by contact with gastric juice increases the volume of the composition, which results in an increased residence time at the gastric level of the gastrointestinal tract (col. 2, lines 38-46).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

- (1) There would have been no motivation to have combined the teachings of Rork *et al.* with the teachings of Conte *et al.***

There is no motivation to combine the teachings of Rork *et al.* and Conte *et al.* because each reference discusses a pharmaceutical composition that is not complementary to the other. Rork *et al.* teaches a tablet coated with a material that is impermeable to water and also impermeable to the selected product, drugs, polymer hydration modulating agents, or to other compounds in the device. This impermeable material is insoluble in body fluids and non-erodible. Apertures are cut in the coating to expose the core, and allow solution to make contact only with exposed portions of the core when in use. The number, size and configuration of the apertures is chosen to provide the release rate required to suit a pharmacologically recognized requirement since the hydration of the polymer will occur only where the apertures allow such core-solvent contact.

Conte *et al.* teaches a multi-layered tablet for providing controlled release of active ingredients exhibiting an absorption window in the first portion of the gastrointestinal tract, *i.e.* substances that are more effectively absorbed only in the stomach, duodenum and in the first portion of the small intestine. The multi-layered tablet includes at least one outer layer consisting of erodible and/or gellable and/or swellable hydrophilic polymers. This layer is characterized in that it can rapidly swell, *i.e.* can markedly and rapidly increase in volume, thereby increasing its residence time in the stomach. Furthermore, this layer may have particular bioadhesive properties allowing the adhesion of the dosage form to the mucosa of the gastrointestinal tract or, by swelling, may also cause the dosage form to float on the gastric juice, resulting in an increased residence time at the gastric level of the gastrointestinal tract. The rate of release of the active ingredient depends on the polymeric substances used to prepare the layers, and these polymers are selected to be slowly soluble and/or slowly gellable and/or erodible and/or at least partially swellable, either rapidly or at different rates. Conte *et al.* teaches that cross-linked polyvinylpyrrolidone is a "superdisgregating polymer" that is incorporated into the outer layer of the tablet to cause a rapid and considerable volume increase of the pharmaceutical form, which prolongs the residence of the pharmaceutical form in the stomach and/or the first tract of the intestine.

Hence, the dosage form of Rork *et al.* and the dosage form of Conte *et al.* are complete pharmaceutical dosage forms unto themselves and are mutually exclusive. There would have been no motivation to have combined or replaced the dosage form of Rork *et al.* with the dosage form as taught by Conte *et al.*

- (2) **Notwithstanding the lack of motivation, the combination of teachings of Rork *et al.* with the teachings of Conte *et al.* does not result in the instantly claimed subject matter.**

Cross-linked polyvinylpyrrolidone

The Examiner alleges that combining the dosage form as taught by Conte *et al.* with the dosage form taught by Rork *et al.* results in the instantly claimed hydrostatic delivery system. Applicant respectfully disagrees. The instantly claimed hydrostatic delivery system of claim 1 includes a homogeneous mixture of a hydrostatic couple comprising one, or more than one hydrodynamic fluid-imbibing polymer that includes one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol and one, or more than one hydrostatic pressure-modulating agent comprising one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone and an agent of interest. None of the layers of the dosage forms of Rork *et al.* or Conte *et al.* include a homogeneous mixture of an agent of interest, an acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol and a cross-linked polyvinylpyrrolidone.

The Examiner states that Rork *et al.* does not teach or suggest cross-linked polyvinylpyrrolidone (see Office Action, page 6). The Examiner alleges that Example 4 of Conte *et al.* cures this defect, because Example 4 describes a formulation that includes cross-linked polyvinylpyrrolidone. Applicant respectfully disagrees. The dosage form of Example 4 of Conte *et al.* includes three layers – a swellable layer, a controlled release layer and a “fast release” layer. The only layer of Conte *et al.* that includes an agent of interest and cross-linked polyvinylpyrrolidone is the “fast release” layer. However, the “fast release” layer of Conte *et al.* is not a homogenous mixture of a hydrostatic couple and an agent of interest as instantly claimed. Conte *et al.* teaches that its “fast release” layer is a mixture of active ingredient and microcrystalline cellulose, which is agglomerated using a solution of polyvinylpyrrolidone, and after drying, the agglomerated granules are compressed into tablets using cross-linked polyvinylpyrrolidone as a binding agent (col. 17, lines 8-20). There is no teaching or suggestion in Conte *et al.* to form a homogeneous mixture that includes a cross-linked polyvinylpyrrolidone, an agent of interest and a hydrodynamic fluid-imbibing polymer

as instantly claimed. Conte *et al.* teaches that cross-linked polyvinylpyrrolidone is a “super-disintegrating polymer” and that such polymers are included in the outer layers (layer 22 and sometimes layer 26) of its dosage form, not in the controlled release layer (see col. 6, lines 4-20). Conte *et al.* does not include cross-linked polyvinylpyrrolidone among the polymeric substances used to prepare the inner controlled release layer (layer 22) (col. 5, lines 50-67). Thus, combining the teachings of Rork *et al.* and Conte *et al.* do not result in the instantly claimed hydrostatic delivery systems.

Improper use of hindsight reconstruction

The only way to combine the teachings of Rork *et al.* and Conte *et al.* to result in the instantly claim hydrostatic delivery system is to use the instant application as a guide, which requires the improper use of hindsight reconstruction. The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. *In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). “To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher” *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). In this instance, it appears that the Examiner is suggesting that the controlled release inner core of Rork *et al.* be combined with the fast release outer layer of Conte *et al.* in order to result in the instantly claimed hydrostatic delivery system. Neither Rork *et al.* nor Conte *et al.* provides a teaching or suggestion to the person of ordinary skill in the art to include the cross-linked polyvinylpyrrolidone of the “fast release” layer of Conte *et al.* in the controlled release layers or Rork *et al.* Applicant respectfully submits that one of skill in the art would not be led to such a combination because introducing a “fast release” system into the controlled release core of Rork *et al.* would change the principle of operation of the controlled release layer of Rork *et al.* by accelerating the release of the active agent. It is the instant Applicant who discovered the value of selecting a homogeneous combination of one or more than one cross-linked hydrodynamic fluid-imbibing polymer and one or more than one cross-linked hydrostatic pressure modulating agent with an agent of interest to produce a hydrostatic couple for a controlled release dosage form. Neither Rork *et al.* nor Conte *et al.* provides any teaching or suggestion to make any of the changes that would produce the claimed product. As noted above, it is improper to use hindsight or the application at issue to combine the references to produce the claimed subject matter.

Zero-order or near zero-order release kinetics

Further, there are other deficiencies in the teachings of the cited art, whether taken alone or in combination. The instantly claimed hydrostatic delivery systems include a hydrostatic couple that results in a controlled release of the agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Applicant respectfully submits that Rork *et al.* teaches that the rate of release of an agent from its dosage form is determined by the selection of the size and number of apertures through its water-impermeable coating, which subsequently expose the surface of the core to the environment (col. 11, lines 52-55). There is no teaching or suggestion that a zero order controlled release of an agent of interest can be achieved by eliminating the water impermeable coating of Rork *et al.*, nor is there any guidance for selecting a combination of ingredients that when combined in a drug delivery system in the form of a homogeneous mixture will release an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

Conte *et al.* does not cure this defect. Conte *et al.* does not teach or suggest a dosage form that releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Conte *et al.* teaches dosage forms for the extended release in the stomach of active ingredients that exhibit a small absorption window in the first portion of the gastrointestinal tract, *i.e.* the stomach, duodenum and in the first portion of the small intestine. Conte *et al.* actually teaches away from prior art controlled release systems having zero order kinetics, stating that such systems uniformly liberate the active ingredient throughout the gastrointestinal tract, including the small intestine and the large intestine, where most of the drug released cannot be absorbed (col. 1, lines 33-47). Conte *et al.* teaches that its dosage form is formulated to increase the residence time in the stomach in order to increase the release of the active ingredient in the gastric level of the gastrointestinal system.

Conte *et al.* teaches that cross-linked polyvinylpyrrolidone is exemplary of a highly swellable (superdisintegrating) polymer that, when it comes in to contact with gastric juice, rapidly swells, resulting in an increase by at least 50% of the total volume of the tablet. Thus, in light of the teachings of Conte *et al.*, one of ordinary skill in the art would expect that including a cross-linked polyvinylpyrrolidone in the dosage form taught by Rork *et al.* would

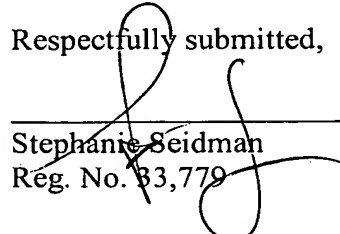
result in the rapid hydration and concomitant expansion of the polymers within the water insoluble, water impermeable polymeric coating. It follows that this rapid expansion would result in either an increased expulsion of the microscopic gel beads from the dosage core of Rork *et al.* or potential rupture of the coating. This would increase the rate of active ingredient release from the dosage, and the release of the agent of interest would not be in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system.

Hence, combining the teachings of Rork *et al.* and Conte *et al.* does not teach or suggest every element of claims 1, 40 and 41. Neither Rork *et al.* nor Conte *et al.*, singly or in combination, teaches or suggests a hydrostatic delivery system that releases an agent of interest in a controlled manner with a zero-order or near zero-order release kinetics over a therapeutically practical time period following administration of the hydrostatic delivery system. Claims 3-8, 10-12, 14-32, 34 and 35 ultimately depend from claim 1 and include the limitations thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claims 1, 3-8, 10-12, 14-32, 34, 35, 40 and 41. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,



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